Full Text AR-95-004

PROGRAM ON MECHANISMS FOR IMMUNOTHERAPY IN RHEUMATIC DISEASES

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RFA: AR-95-004

P.T.

Keywords:

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Letter of Intent Receipt Date: April 12, 1995
Application Receipt Date: July 12, 1995

APPLICANTS RESPONDING TO THIS RFA WILL BE ASKED TO USE A MODIFIED (ABBREVIATED) GRANT APPLICATION FORMAT; SPECIFIC INSTRUCTIONS FOR COMPLETING THE APPLICATION ARE IN THE APPLICATION PROCEDURES BELOW.

PURPOSE

The Rheumatic Diseases Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) invites applications for small basic research projects linked to separately funded ongoing or completed clinical trials of new and innovative immunotherapies in rheumatic diseases. The aim of the basic research projects will be to identify the mechanisms related to the efficacy of the therapy or to demonstrate the relevance of new or known pathogenic mechanisms leading to target tissue injury. Projects that apply current basic science approaches to the study of the mechanisms of immunotherapies through formal collaborations are strongly encouraged.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority

areas. This RFA, Program on Mechanisms of Immunotherapy in Rheumatic Diseases, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) individual research project grant (R01). Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for each application submitted in response to the present RFA may not exceed three years. The anticipated earliest award date is March 1, 1996. This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications.

FUNDS AVAILABLE

The estimated funds (total costs) available for the first year of support for the entire program is $450,000. Because the nature and scope of the research sought by this RFA are narrowly defined, the size of an award will not exceed $50,000 direct cost for the first year with four percent escalation in years two and three. Funding is contingent upon receipt of scientifically meritorious applications. The NIAMS expects to make six new awards.

RESEARCH OBJECTIVES

Background

The development of biologics and the availability of technology to produce antigen peptides and other analogues of molecules mediating immune responses and inflammation, together with recent advances in the characterization of some critical steps in the pathogenesis of rheumatic

diseases, have led to a surge of new and innovative therapies for these chronic and debilitating disorders. Primarily under the sponsorship of the private sector and the FDA, many of these new agents are being tested for safety and efficacy in patients with rheumatoid arthritis and systemic lupus erythematosus.

Although the results of some of these trials have been promising, the limited support given to ancillary basic research aimed at explaining the mechanisms by which the therapies may be effective, has hampered progress in designing improved administration modalities and regimens. In addition, opportunities to gain insights into the pathogenesis of the diseases by studying the host responses under controlled experimental treatments and valuable clinical specimens useful for future studies may not have been realized. The purpose of this RFA is to provide an opportunity for support of small ancillary basic research projects linked to ongoing or completed clinical trials of new and innovative immunotherapy of rheumatic diseases. The objective of this program is to allow investigators to: (1) conduct pilot or small research projects to collect limited but definitive information about the underlying mechanisms of immunotherapy; (2) gather enough preliminary data needed to proceed to a new design for an ongoing clinical trial; or (3) collect data leading to submission of a regular individual research grant application.

Although a number of scientific projects may be possible under this RFA, the following areas are of special interest:

o Mechanisms of action of immunotherapies involving the use of monoclonal antibodies directed against cytocines, cytokine receptors, and cytokine-receptor antagonists;

o Mechanism of action of non-depleting monoclonal antibodies;

o Studies involving the use of antigens or antigen-peptides for induction of tolerance;

o Mechanisms involved in the effects of agents that may affect the expression and/or function of adhesion molecules, such as small molecular weight analogues, monoclonal antibodies and carbohydrates; and

o Effects of T cell receptor peptide vaccines.

Within the context of these studies, research aimed at investigating either the mechanisms underlying the therapeutic effect or immune and inflammatory responses that may serve as markers of therapeutic response are encouraged. Projects exploring critical steps in the

pathogenesis of disease progression that are amenable to be studied under the experimental conditions created by the new immunotherapy are possible.

This list is illustrative and not exclusive or restrictive. Collaborations between basic research teams with experience in basic and molecular immunology and clinical researcher are highly encouraged.

NOTE: Investigators who are considering the submission of an application under this program may wish to review the related RFA: "Mechanisms of Immunotherapy in Autoimmune Diseases". Further information regarding eligibility for each of the RFAs can be obtained from the Program staff listed under INQUIRIES.

Investigators proposing to utilize the patient populations from clinical trials must first obtain permission from the ancillary studies committees of the appropriate trial. Applications must include written approval by the appropriate Study Group of the ongoing trial for which basic research studies are being proposed under this RFA.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43) and supersedes and strengthens the previous policies (Concerning the Inclusion of Women in Study Populations, and Concerning the Inclusion of Minorities in Study Populations), which have been in effect since 1990. The new policy contains some new provisions that are substantially different from the 1990 policies.

All investigators proposing research involving human subjects should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," which were published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and reprinted in the NIH Guide for Grants and Contracts of March 18, 1994, Volume 23, Number 11.

Investigators may obtain copies from these sources or from the program staff or contact person listed under INQUIRES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Submit applications on form PHS 398 (rev. 9/91), the application form for the traditional research project grant. This form is available in an applicant institution's office of sponsored research and from the Office of Grants Information, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Room 449, Bethesda, MD 20892, telephone (301) 435-0714. Use the following format for research project grant applications and ensure the points identified in the section, "Review Procedures and Criteria" are fulfilled. To identify the application as a response to this RFA, check "YES" on item 2a of page 1 of the application and enter the title "Program on Mechanisms of Immunotherapy in Rheumatic Diseases", AR-95-004.

Applicants are expected to conform to the 20-page limit. Appendices containing supporting materials may be submitted with the application, but may not be used to circumvent this requirement.

The RFA label available in the PHS 398 (rev. 9/91) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2a of the face page of the application form and the YES box must be marked.

The following modifications are to be made to the standard PHS 398 application instructions:

o INITIAL BUDGET PERIOD - Only the names of personnel and level of effort should be itemized in the Personnel section of the "Detailed Budget for the Initial Budget Period" (Form Page 4). In addition, generally list consultants, equipment, supplies, travel, patient care activities, alterations and renovations and other needs, as appropriate. No costs need be associated with these individual items or categories. If Consortium/Contractual Costs are requested, then the "Subtotal Direct Costs" line should be completed and the "Consortium/Contractual Costs" section should include all Contractual direct, indirect and total costs. The "Total Direct Cost" line at the bottom of the page must be completed. The maximum amount that may be requested is $50,000 in the first year. Escalation in future years may not exceed four percent.

APPLICATIONS NOT CONFORMING TO THESE GUIDELINES WILL BE CONSIDERED UNRESPONSIVE TO THIS RFA AND WILL BE RETURNED WITHOUT FURTHER REVIEW.

o BIOGRAPHICAL SKETCH - In addition to the standard information requested on Form Page 6, the applicant has the option of providing the title and source of any sponsored support relevant to the proposed research.

o OTHER SUPPORT - No other support information is required on "Other Support" pages (Form Page 7). Selected other support information relevant to the proposed research may be included in the Biographical Sketch as indicated above. Complete other support information will be requested by NIAMS staff upon consideration for an award.

o CHECKLIST - No "checklist" page is required as part of the NIAMS application. A completed Checklist page will be requested by NIAMS staff upon consideration for an award.

Research Plan (Booklet Pages 19-24): Note: Items 1-4 may not exceed 20 pages.

o Item 1 - Specific Aims (typically less than one page): List in priority order the broad, long range objectives of the proposed project and describe concisely and realistically the hypothesis to be tested and what the specific research described in this application is intended to accomplish.

o Items 3 - 4: Complete as instructed on pages 21-23 of the PHS 398 booklet, noting the reduced page limit stated above. The following is general guidance for information to be presented in this section:

- Preliminary studies pertinent to the application.
- Rationale for each particular set of experiments.
- General methods that will be utilized. Provide specific details ONLY for those techniques that are unique, or where a significant departure from a generally accepted technique is important for the reviewers to know.
- Outcome measures that will be used to assess the success or failure of each set of experiments.
- Potential pitfalls in the experimental design and alternative studies that will be done if the proposed experiments fail.

o Items 5 - 6: Complete as described on pages 22-23 of PHS 398 booklet.

o Item 7 - Consultants/Collaborators: Biographical sketches should conform to the brief format described for Form FF, above.

o Item 8 - Consortium, Contractual Arrangements (1 page only): Provide brief explanation (not to exceed one page) of the scientific, fiscal, and administrative arrangements made with collaborating organizations.

Appendix (PHS 398 Booklet - Page 24) A maximum of five publications, manuscripts, submitted or accepted for publication, patents, invention reports may be included. Other than this change, complete as instructed.

Forms II and JJ - Checklist: Do not complete. Information will be requested by NIAMS only from applicants being considered for funding.

Submit a signed, typewritten original of the application, and three signed photocopies, in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At the time of submission, two additional copies of the application must also be sent to Dr. Tommy Broadwater at the address listed under INQUIRIES.

Applications must be received by July 12, 1995. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

LETTER OF INTENT

Prospective applicants are asked to submit, by April 12, 1995, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the

Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIAMS staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to Susana A. S. Sztein, M.D. at the address listed under INQUIRIES.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by DRG and responsiveness by NIAMS staff. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, DRG staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle. Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIAMS in accordance to the review criteria listed below.

As part of the initial merit review, a process (triage) may be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other applications received in response to the RFA. Applications judged to be competitive will be discussed and be assigned a priority score. Applications determined non-competitive will be withdrawn from further consideration and the Principal Investigator and the official signing for the applicant organization will be notified. The second level of review will be provided by the NIAMS Advisory Council.

Review criteria for this RFA are generally the same as those for unsolicited research grant applications:

o scientific, technical, or clinical significance and originality of proposed research;

o appropriateness and adequacy of the experimental approach and methodology proposed to carry out the research;

o qualifications and research experience of the Principal Investigator and staff and collaborations;

o availability of the resources necessary to perform the research;

o appropriateness of the proposed budget and duration in relation to the proposed research and within the limits set in the RFA; and

o adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. The initial review group will also examine the provisions for the protection of human and animal subjects, the safety of the research environment, and conformance with the NIH Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research.

AWARD CRITERIA

The anticipated date of award is March 1, 1996. Awards will be based upon the following criteria:

o availability of funds;
o relevance of clinical trial and programmatic priorities of the NIAMS; and
o responsiveness to the RFA.

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues and address the letter of intent to:

Susana A. S. Sztein, M.D.
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS-37G
45 Center Drive MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-5032
FAX: (310) 480-4543

Email: arthrit@ep.niams.nih.gov

Direct inquiries regarding fiscal matters to:

Diane Watson
Grants Management Office
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS-49J
45 Center Drive MSC 6500
Bethesda, MD 20892-6500
Telephone: (310) 594-3505
FAX: (310) 480-5450
Email: watsond@ep.niams.nih.gov

Direct inquiries regarding review issues and address two copies of the application to:

Tommy L. Broadwater, Ph.D.
Grants Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Natcher Building, Room 5AS-25U
45 Center Drive MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX: (301) 480-4543
Email: broadwat@ep.niams.nih.gov

Schedule

Letter of Intent Receipt Date: April 12, 1995
Application Receipt Date: July 12, 1995
Initial Review: October 1995
Second Level Review: January 1996
Anticipated Award Date: March 1996

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.361. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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